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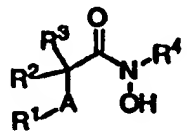
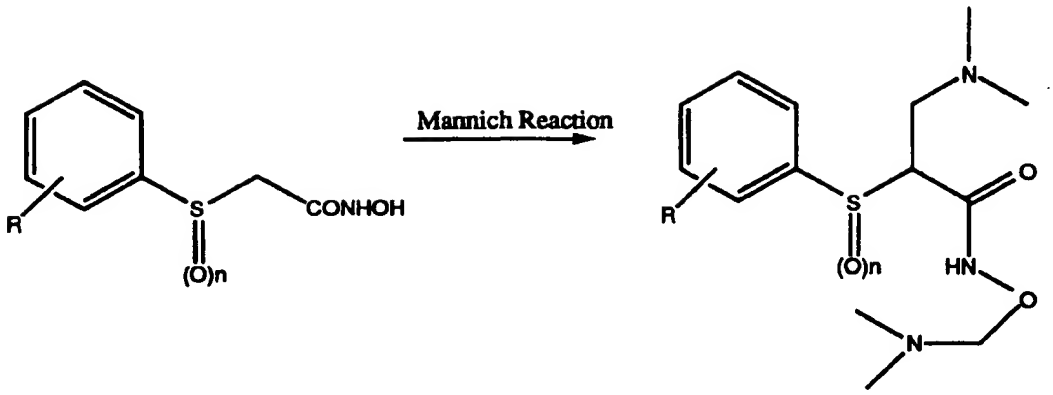
(54) Title: N–HYDROXY–2–(ALKYL, ARYL OR HETEROARYL SULFANYL, SULFINYL OR SULFONYL)–3–SUBSTITUTED ALKYL, ARYL OR HETEROARYLAMIDES AS MATRIX METALLOPROTEINASE INHIBITORS

(57) Abstract

Matrix metalloproteinases (MMPs) are a group of enzymes that have been implicated in the pathological destruction of connective tissue and basement membranes. These zinc containing endopeptidases consist of several subsets of enzymes including collagenases, stromelysins and gelatinases. TNF–α converting enzyme (TACE), a pro–inflammatory cytokine, catalyzes the formation of TNF–α from membrane bound TNF–α precursor protein. It is expected that small molecule inhibitors of MMPs and TACE therefore have the potential for treating a variety of disease states. The present invention provides low molecular weight, non–peptide inhibitors of matrix metalloproteinases (MMPs) and TNF–α converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection having formula (I) wherein R^2 and R^3 form a heterocyclic ring and A is S, S(O), or $S(O)_2$, and R^1 and R^4 are defined herein.



(I)



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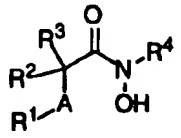
Some sulfone carboxylic acids are disclosed in U.S. patent 4,933,367. Those compounds were shown to exhibit hypoglycemic activity.

SUMMARY OF THE INVENTION:

The present invention relates to novel, low molecular weight, non-peptide inhibitors of matrix metalloproteinases (MMPs) and TNF-α converting enzyme (TACE) for the treatment of arthritis, tumor metastasis, tissue ulceration, abnormal wound healing, periodontal disease, bone disease, diabetes (insulin resistance) and HIV infection.

In accordance with this invention there is provided a group of compounds of general formula I



I

wherein:

R^1 is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

aryl of 6 to 10 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, optionally substituted with one or two groups selected independently from R^5;

or heteroaryl-$(CH_2)_{0-6}$- wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be optionally substituted with one or two groups selected independently from R^5;

A is -S-, -SO- or SO_2-;

R^2 and R^3, taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, optionally substituted with one or two groups selected independently from R^5;

R^5 is H, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, F, Cl, Br, I, CN, CHO, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1–C_6 alkoxyaryl, C_1–C_6 alkoxyheteroaryl, C_1-C_6 alkylamino-C_1-C_6 alkoxy, C_1-C_2 alkylene dioxy, aryloxy-C_1–C_6 alkyl amine, C_1-C_{12}

perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, $-NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl,SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$-C_1–C_6 alkyl $S(O)_n$ aryl where n is 0, 1 or 2;, or COheteroaryl, wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COO-C_1-C_6-alkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$, SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, CONHSO-C_1-C_6-alkyl, $CONHSO_2$aryl, aryl, or heteroaryl, where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C_1–C_6 alkyl;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

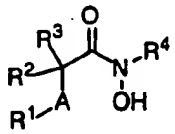
cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein the cycloalkyl or bicycloalkyl group is optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or N-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5; or

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

A more preferred aspect of the present invention is the group of compounds of general formula (Ia):



Ia

wherein:

R^1 is alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

aryl of 6 to 10 carbon atoms, optionally substituted with one to two groups selected independently from R^5;

cycloalkyl of 3 to 8 carbon atoms, optionally substituted with one to two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle of from 5 to 10 members containing one heteroatom selected from O, S or NR^7, optionally substituted with one to two groups selected independently from R^5;

or heteroaryl-$(CH_2)_{0-6}$- wherein the heteroaryl group is 5 to 6 membered with one or two heteroatoms selected independently from O, S, and N and may be optionally substituted with one or two groups selected independently from R^5;

A is -S-, -SO- or SO_2-;

R^2 and R^3, taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

R^5 is H, F, Cl, Br, I, CN, CHO, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1–C_6 alkoxyaryl, C_1–C_6 alkoxyheteroaryl, C_1-C_6-alkylamino-C_1-C_6 alkoxy, C_1-C_2-alkylene dioxy, aryloxy-C_1-C_6 alkyl amine, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO-C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO-C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, $NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl,

$CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; or saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$ alkyl or aryl where n is 0, 1, or 2; or COheteroaryl;

wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$,SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$alkyl, $CONHSO_2$aryl, aryl, heteroaryl; wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, wherein biphenyl is optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, wherein aryl is optionally substituted with one or two groups selected independently from R^5;

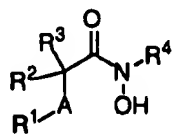
cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, wherein cycloalkyl or bicycloalkyl is optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or N-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5;

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred group of compounds are those of the following formula (Ib):



Ib

in which

R^1 is phenyl, naphthyl, alkyl of 1-18 carbon atoms or heteroaryl such as pyridyl, thienyl, imidazolyl or furanyl, optionally substituted with C_1–C_6 alkyl, C_1-C_6 alkoxy, C_6-C_{10} aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, halogen; or $S(O)_n$ - -C_1–C_6alkyl C_1–C_6 alkoxyaryl or C_1–C_6 alkoxyheteroaryl;

A is -S-, -SO- or -SO_2-;

R^2 and R^3 , taken with the carbon atom to which they are attached, form a 5 to 7 membered heterocyclic ring containing O, S or N-R^7 optionally having one or two double bonds;

R^4 is hydrogen,

alkyl of 1 to 6 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

phenyl or naphthyl optionally substituted with one or two groups selected independently from R^5;

C_3 to C_8 cycloalkyl or bicycloalkyl optionally substituted with one or two groups selected independently from R^5;

R^5 is H, C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2-C_{12} alkynyl, F, Cl, Br, I, CN, CHO, C_1-C_6 alkoxy, aryloxy, heteroaryloxy, C_3-C_6 alkenyloxy, C_3-C_6 alkynyloxy, C_1-C_6 alkylamino-C_1-C_6 alkoxy, C_1-C_2 alkylene dioxy, aryloxy-C_1–C_6 alkyl amine, C_1-C_{12} perfluoro alkyl, $S(O)_n$-C_1-C_6 alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; OCOO C_1-C_6 alkyl, OCOOaryl, $OCONR^6$, COOH, COO C_1-C_6 alkyl, COOaryl, $CONR^6R^6$, CONHOH, NR^6R^6, $SO_2NR^6R^6$, NR^6SO_2aryl, $-NR^6CONR^6R^6$, $NHSO_2CF_3$, SO_2NHheteroaryl,SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, SO_2NHCOaryl, $CONHSO_2$-C_1-C_6 alkyl, $CONHSO_2$aryl, NH_2, OH, aryl, heteroaryl, C_3 to C_8 cycloalkyl; saturated or unsaturated 5 to 10 membered mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR^7, wherein C_1–C_6 alkyl is straight or branched, heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

R^6 is H, C_1 to C_{18} alkyl optionally substituted with OH; C_3 to C_6 alkenyl, C_3 to C_6 alkynyl, C_1 to C_6 perfluoro alkyl, $S(O)_n$ alkyl or aryl where n is 0, 1 or 2; or COheteroaryl; wherein heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or NR^7 and aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy;

and R^7 is C_7–C_{11} aroyl, C_2–C_6 alkanoyl, C_1-C_{12} perfluoro alkyl, $S(O)_n$-alkyl, $S(O)_n$-aryl where n is 0, 1 or 2; COOalkyl, COOaryl, $CONHR^6$, $CONR^6R^6$, CONHOH, $SO_2NR^6R^6$, SO_2CF_3, SO_2NHheteroaryl, SO_2NHCOaryl, $CONHSO_2$alkyl, $CONHSO_2$aryl, aryl, or heteroaryl; where aryl is phenyl or naphthyl, optionally substituted by 1 or 2 groups selected independently from halogen, cyano, amino, nitro, C_1–C_6 alkyl, C_1–C_6 alkoxy, or hydroxy; and heteroaryl is a 5-10 membered mono or bicyclic heteroaryl group having 1 to 3 heteroatoms selected independently from O, S or N-C_1–C_6 alkyl;

alkyl of 1 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

alkenyl of 3 to 18 carbon atoms having from 1 to 3 double bonds, optionally substituted with one or two groups selected independently from R^5;

alkynyl of 3 to 18 carbon atoms having from 1 to 3 triple bonds, optionally substituted with one or two groups selected independently from R^5;

arylalkyl of 7 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

biphenylalkyl of 13 to 18 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

arylalkenyl of 8 to 16 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

cycloalkylalkyl or bicycloalkylalkyl of 4 to 12 carbon atoms, optionally substituted with one or two groups selected independently from R^5;

saturated or unsaturated mono or bicyclic heterocycle containing one heteroatom selected from O, S or NR-C_1–C_6 alkyl, optionally substituted with one or two groups selected independently from R^5;

R^8R^9N-C_1-C_6-alkoxyaryl-C_1-C_6-alkyl where R^8 and R^9 are independently selected from C_1-C_6 alkyl or R^8 and R^9 together with the interposed nitrogen forms a 5-7 membered saturated heterocyclic ring optionally containing an oxygen atom, wherein the aryl group is phenyl or naphthyl;

and the pharmaceutically acceptable salts thereof.

The most preferred matrix metalloproteinase and TACE inhibiting compounds of this invention are:

1-benzyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide,

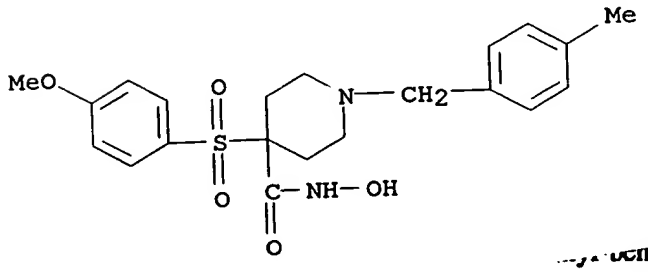
J=.029, 2H), 7.72-7.75 (d, J=.027, 2H), 7.87 (s, 1H), 9.37 (s, 1H), 10.53 (s, 1H), 11.18 (s, 1H).

Example 86

4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide

Page 1

IN 4-Piperidinecarboxamide, N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]-1-[(4-methylphenyl)methyl]- (9CI)
MF C21 H26 N2 O5 S



...benzyl)-piperidine-4-carboxylic acid was prepared starting from 4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (4.3g, 9.9 mmol) dissolve in methanol (30 mL) , 10 N sodium hydroxide (10 mL), tetrahydrohydrofuran (20 mL). The resulting reaction mixture was worked up as outlined in example 83. Yield 1.6 g (40 %). white solid mp 207-208 °C , MS: 404.3 $(M+H)^+$.

Starting from 4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid (1.59g, 3.9 mmol) and following the procedure as outlined in example 83, .505 g of 4-(4-methoxy-benzenesulfonyl)-1-(4-methylbenzyl)-piperidine-4-carboxylic acid hydroxamide was isolated as a white solid. mp 176-177 °C; Yield 32%; MS: 419.0 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.24-2.32 (m, 2H), 2.51(t, 3H), 2.73-2.80 (m, 2H), 3.35-3.50 (m, 4H), 3.87 (s, 3H), 4.24 (s, 2H), 7.13-7.17 (d, J=.039, 2H), 7.23-7.60 (d, J=.036, 2H), 7.38-7.41 (d, J=.025, 2H), 7.65-7.68 (d, J=.039, 2H).

cyclooctyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as a white powder. Yield 22%; mp >200 °C; MS: 425 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 1.42-1.66 (m, 14H), 1.83 (m, 2H), 2.33 (m, 2H), 2.67 (m, 2H), 3.30-3.51 (m, 3H) 3.88 (s, 3H) 7.17 (d, 2H), 7.66 (d, 2H).

Example 95

1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example 83. Starting from 4-(methoxy-benzenesulfonyl) acetic acid ethyl ester (3 g, 11.6 mmol) and ethyl-bis-(2-chloro-ethyl)-amine (2.39g, 11.6 mmol). Yield 3.09 g, (75%); low melting brown solid; MS: 356 $(M+H)^+$.

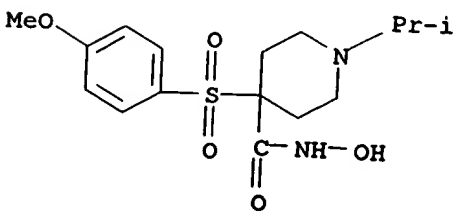
1-Ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid was prepared starting from 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (2.42 g, 6.8 mmol) dissolved in methanol (100 ml) and 10 N NaOH (15 ml). The resulting reaction mixture was worked up as outlined in example 83. Yield 1.29 g (58%); white solid; mp 209 °C; MS: 328 $(M+H)^+$.

Starting from 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid (1.23 g, 3.76 mmol) and following the procedure as outlined in example 83, 1.02 g of 1-ethyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off white powder. Yield 80%; mp 85 °C; MS: 343 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 0.926 (t, J =7.1 Hz, 3H), 1.68-1.89 (m, 4H), 2.05-2.24 (m, 4H), 2.73 (q, 2H), 3.85 (s, 3H), 7.07 (d, 2H), 7.64 (d, 2H).

Example 96

1-Isopropyl-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

IN 4-Piperidinecarboxamide, N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]-1-(1-methylethyl)- (9CI)
MF C16 H24 N2 O5 S



Example 98

1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester was prepared according to the general method as outlined in example 83. Starting from from 4-(butoxy-benzenesulfonyl) acetic acid ethyl ester (6 g. 20 mmol) and bis-(2-chloro-ethyl)-benzylamine (10 g, 30 mmol). Yield 5.15 g (56%); yellow oil; MS: 460 $(M+H)^+$.

1-Benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid was prepared starting from 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid ethyl ester (5.1 g, 11.1 mmol) dissolved in THF:methanol 3:1 and 10 N NaOH (10 ml). The resulting reaction mixture was worked up as outlined in example 83. Yield 2.66 g (56%); off white solid; mp 210 °C; MS: 432 $(M+H)^+$.

Starting from 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid (2.61 g, 6.06 mmol) and following the procedure as outlined in example 83, 860 mg of 1-benzyl-4-(4-butoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide was isolated as an off white powder. Yield 32%; mp 144 °C; MS: 446.9 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6): δ 0.94 (t, J = 7.3 Hz, 3H), 1.44 (q, J = 7.5 Hz, 2H), 1.70 (q, 2H), 2.28-2.32 (m, 2H), 2.50 (d, 2H), 2.74-2.83 (m, 2H), 3.35 (d, 2H), 4.08 (t, J = 6.3 Hz, 2H), 4.34 (s, 2H), 7.13 (d, J = 8.7, 2H), 7.45 (s, 3H), 7.54 (s, 2H), 7.74 (d, J = 8.7, 2H), 9.35 (s, 1H), 10.7 (s, 1H).

Example 99

1-(4-Fluoro-benzyl)-4-(4-methoxy-benzenesulfonyl)-piperidine-4-carboxylic acid hydroxyamide

IN 4-Piperidinecarboxamide, 1-[(4-fluorophenyl)methyl]-N-hydroxy-4-[(4-methoxyphenyl)sulfonyl]- (9CI)

MF C20 H23 F N2 O5 S